World Journal of Biology Pharmacy and Health Sciences
eISSN: 2582-5542
Cross Ref DOI: 10.30574/wjbphs
Journal homepage: https://wjbphs.com/

(RESEARCH ARTICLE)

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Formulation and evaluation of Liquisolid compact of Nitrofurantoin

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World Journal of Biology Pharmacy and Health Sciences, 2025, 22(03), 266-276

Publication history: Received on 17 April 2025; revised on 29 May 2025; accepted on 01 June 2025

Article DOI: https://doi.org/10.30574/wjbphs.2025.22.3.0542

Abstract

This study focuses on improving the solubility and dissolution rate of Nitrofurantoin, a water-insoluble antimicrobial agent, using the liquisolid compact technique. Liquisolid technology offers a promising approach to enhance the bioavailability of poorly soluble, lipophilic drugs by converting them into dry, free-flowing, and compressible powder blends. In this research, Nitrofurantoin was dissolved in various non-volatile solvents such as Tween 20 and PEG 400 to create liquid drug formulations. These formulations were then adsorbed onto carrier materials like microcrystalline cellulose and coated with Talc to produce liquisolid powders. The resulting tablets were evaluated for both pre-compression (flow properties) and post-compression characteristics, including hardness, friability, disintegration time, and *in vitro* drug release. Results demonstrated a significant improvement in the dissolution rate of Nitrofurantoin from the liquisolid tablets compared to those prepared by direct compression. This enhancement is likely due to the increased surface area, improved wetting, and better solubilization of the drug in the chosen non-volatile solvents. Overall, the study confirms that the liquisolid compact technique is an effective and practical strategy to enhance the dissolution profile of Nitrofurantoin, which may lead to improved therapeutic outcomes.

Keywords: Liquisolid compact; Dissolution rate; Solubility enhancement; Poorly water soluble drugs; Bioavailability

1. Introduction

Liquisolid systems are innovative drug delivery formulations where liquid medications are converted into dry, free-flowing, and compressible powders. This approach involves blending liquid lipophilic drugs, drug suspensions, or solutions of poorly water-soluble solid drugs with suitable non-volatile solvents. These are then combined with carrier and coating materials to produce a dry, non-sticky powder blend that can be easily compressed into tablets.

Carrier materials, such as various grades of microcrystalline or amorphous cellulose, serve as the base that absorbs the liquid medication. Coating materials, typically fine silica powders, help improve the flow and compression properties of the final formulation. However, there is a limit to how much liquid can be incorporated beyond a certain point, the blend may lose its desirable flow and compaction characteristics.

1.1. Mechanism of the Liquisolid Technique

The liquisolid technique operates through a combination of absorption and adsorption. When the liquid drug formulation is added to a porous carrier like cellulose, it first gets absorbed into the material's internal structure. The liquid is drawn into the carrier's network of tiny pores and matted fibers. Once the absorption capacity is reached, the excess liquid then adheres to the surface of the particles a process known as adsorption.

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The addition of a coating material, such as colloidal silica, is crucial at this stage. Thanks to its high surface area and excellent adsorptive properties, it wraps around the particles, helping to maintain the flowability and compressibility of the final blend. This dual mechanism ensures that the liquisolid system remains practical for tablet formulation while enhancing drug solubility and bioavailability.

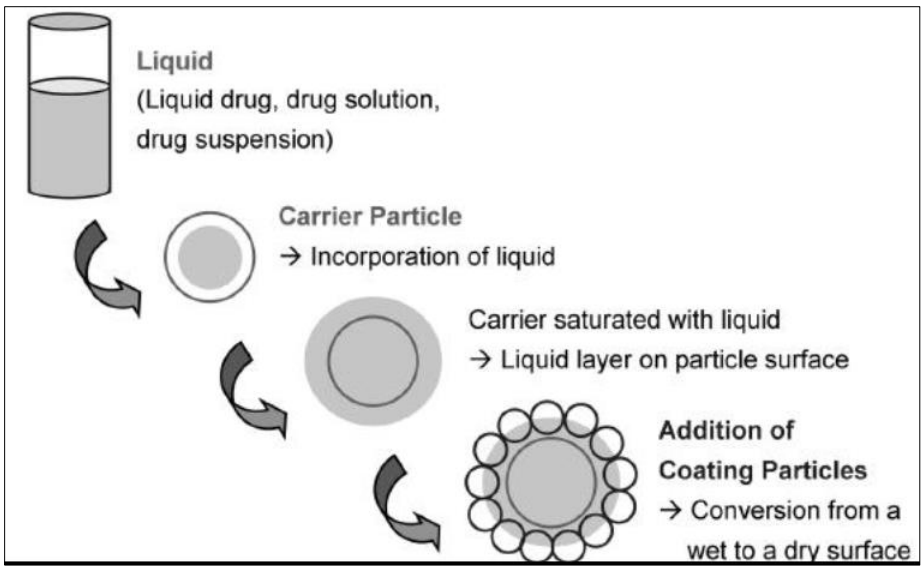

Figure 1 Mechanism of Liquisolid technique

2. Material and Method

2.1. Selection of excipients

Tween 20 was used as liquid vehicle to prepare the liquid medication of the different concentrations. Microcrystalline cellulose was chosen as carrier material because of high surface area of Microcrystalline cellulose (1.18 m^2/g) in comparison with other carriers. Talc was used as coating material. This has high adsorptive properties and large specific area, imparts good flow properties to the liquisolid systems Sodium starch glycolate was used as super disintegrate. Magnesium oxide used as flow activator and Magnesium stearate is used as a lubricant.

2.2. Pre-formulation studies of drug

The following parameters were analyzed to determine the flow properties of the granules:

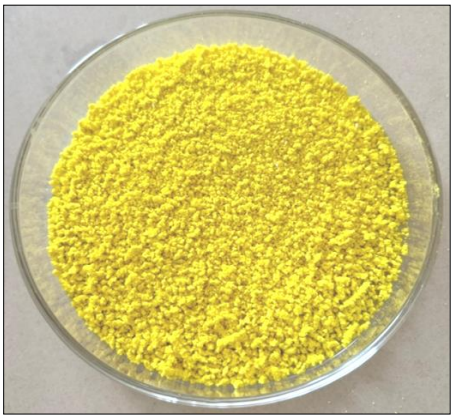

Figure 2 Nitrofurantoin Powder

- Bulk Density: It is the mass of the granules divided by the bulk volume.

- Tapped Density: It is measured after the powder in the graduated cylinder has been mechanically tapped until no further change in volume occurs.
- Angle of Repose: Calculated by the formula:

$$\theta = \tan^{-1}(h/r)$$

where h is the height of the cone and r is the radius of the base.

Figure 3 Angle of Repose

Carr's Index: Computed by the formula:

$$\text{Carr's Index (\%)} = [(\text{Tapped Density} - \text{Bulk Density}) / \text{Tapped Density}] \times 100$$

- Hausner's Ratio: Calculated by the formula:

$$\text{Hausner's Ratio} = \text{Tapped Density} / \text{Bulk Density}$$

Hausner's ratio lower than 1.25 indicates good flow properties.

2.3. Calibration Curve for Nitrofurantoin Using UV Spectroscopy

2.3.1. Preparation of Nitrofurantoin Standard Solution in 0.1N HCl.

Accurately weighed 50 mg of Nitrofurantoin was dissolved in 50 ml of methanol. 10 ml aliquot was withdrawn from the above solution. It was added into a 100-ml volumetric flask, and volume was adjusted with 0.1N HCl up to the mark to get a final stock solution of 100 µg/ml.

2.3.2. Scanning of Nitrofurantoin in 0.1N HCl.

The standard solution of the drug was scanned from 200 nm to 400 nm using a Shimadzu UV-1800 spectrophotometer. The wavelength of maximum absorption (λmax) was noted.

2.3.3. Procedure

Aliquots of 0.2, 0.4, 0.6, 0.8, and 1 ml were taken from the stock standard solution and transferred to 10 ml volumetric flasks; the volume was then made up to 10 ml with 0.1 N HCl; thus, concentrations ranging from 2, 4, 6, 8, to 10 µg/ml were obtained. These solutions were measured for absorbance values at the λmax of 240 nm in the double beam UV-spectrophotometer with blank of 0.1N HCl.

2.4. Formulation

2.4.1. Preparation of liquisolid powder systems

Several liquisolid compacts were prepared as follows. The desired quantities of the previously weighed of the solid drug and the liquid vehicle (Tween 20) were mixed. The solution was then sonicated for 15 min until a homogeneous drug solution was obtained. Subsequently, the calculated weight (W) of the liquid medications (equal to 10 mg drug) were combined with the calculated amounts of the carrier material (Microcrystalline cellulose) (Q) and mixed thoroughly. The resulting wet mass was mixed with the calculated quantity of the coating material (Talc) (q), using a conventional mixing method to give simple admixture. Multiple factors were varied such as the concentrations of the drug in liquid vehicle PEG i.e. 10 %, 15 %, 20 % w/w and carrier: coat ratios (different R values) of which there were a range from 10 to 30 was utilized. Different liquid load factors (Lf) also from 0.230 to 0.292 were utilized. Then 10% magnesium oxide and 5% magnesium stearate were added. Lastly, 5 % w/w of sodium starch glycolate as a disintegrant was added to the above mixture.

2.4.2. Tablet preparation

The final mixture was compressed on a multi mill rotary tablet machine using a flat faced punch and die, size of 12 mm.

2.4.3. Preparation of plain tablet of pure drug

Plain tablets of pure Nitrofurantoin containing 10 mg of the dose were made on a tablet machine.

Table 1 Composition of different Nitrofurantoin liquisolid compacts mathematical model

Drug Concentration in Tween 20	Formulation No.	R Value	Liquid Load Factor (Lf)	MCC (Q) (mg)	Talc (q) (mg)	SSG (mg)	MgO (mg)	Mg Stearate (mg)	Tween 20 (mg)	Total Wt. (mg)
10%	F1	10	0.292	315.31	31.53	21.94	34.55	4.60	82.86	500
	F2	20	0.246	338.65	16.93	21.94	34.56	4.61	74.98	500
	F3	30	0.230	347.41	11.58	21.94	34.56	4.60	71.91	500
15%	F4	10	0.292	314.83	31.47	22.59	34.56	4.61	78.14	500
	F5	20	0.246	338.66	16.92	23.31	34.61	4.61	70.81	500
	F6	30	0.230	346.97	11.56	22.51	34.56	4.60	67.83	500
20%	F7	10	0.292	303.50	30.34	22.00	34.63	4.61	88.62	500
	F8	20	0.246	326.28	16.31	21.94	34.56	4.61	80.26	500
	F9	30	0.230	335.22	11.16	21.94	34.56	4.60	77.10	500

2.5. Post-Compression Evaluation

The compressed tablets were tested for:

- Weight Variation: The procedure started with twenty tablets randomly selected from the design batch. The individual weights of the twenty tablets were determined using a digital balance, and the average weight was calculated. The individual weights were compared to the average weight based on individual tablet deviation of not greater than ±5% standard deviation.
- Thickness: The thickness of ten tablets was measured using a Vernier caliper to evaluate if the thickness was uniform.

Figure 4 Thickness

- Hardness: The hardness of ten tablets was measured using a Monsanto hardness tester to evaluate mechanical strength or hardness.
- Friability: Ten tablets were placed in a Roche friabilator at 100 rpm for 15 minutes in order to exercise abrasion. Tablet weight loss was recorded after dusting and should not be more than 1% as reported in pharmacopoeia.

Figure 5 Friability

Uniformity of Drug Content: Ten tablets were crushed and dissolved in water. After filtration, a portion of the sample was taken and the concentration was determined with a UV spectrophotometer at 233 nm, after dilution.

2.6. *In vitro* drug release

The USP paddle apparatus was utilized for all *in vitro* dissolution studies. 900ml 0.1N HCl was utilized as a dissolution media using 50 rpm and 37 ± 0.5oC. Aliquots were withdrawn at appropriate times (5, 10, 15, 20, 25, 30, 45, and 60 minutes), filtered through what man filter paper, and diluted to 10 ml with 0.1N HCl. Sink conditions were maintained throughout the study. The samples were analyzed by UV/visible spectrophotometer at λ max of 240nm.

2.7. Stability studies

The stability studies for tablets were performed by storing sample tablets from optimized batches for 1 month. The tablets were filled and packaged in aluminum, inside polyethylene coated aluminum and were stored in a stability control oven (Bio techno lab), 40˚C, 75% relative humidity, for 1 month. At the end of 1 month the samples were analyzed for various parameters including: physical appearance, % drug content.

3. Results and Discussion

3.1. Pre-formulation studies of drug

3.1.1. Characterizations of drug

Table 2 Result of Organoleptic property

Drug	Appearance	Observation
Nitrofurantoin	yellow amorphous powder	yellow amorphous powder

3.1.2. Determination of Melting Point:

Table 3 Result of Melting point

Drug	Melting Point	Observation
Nitrofurantoin	268-272°C	270°C

3.1.3. Angle of Repose

Table 4 Result of angle of Repose

Material	Specification	Observation	Result
Nitrofurantoin	N.A.	27.82°	Good Flow Property

3.1.4. Determination of Density

Table 5 Result of Bulk density and Tapped density

Material	Bulk Density	Tapped Density	Result
Nitrofurantoin	0.402	0.518	Fault Fracture Density (FFD)

3.1.5. Powder compressibility

Table 6 Result of powder compressibility

Material	Compressibility Index	Hausner's Ratio
Nitrofurantoin	18.52	1.22

3.1.6. pH of the solution

Table 7 pH of Nitrofurantoin powder

Test	Specification	Observation	Result
Nitrofurantoin	N/A	6.3	Within range

3.1.7. Solubility studies

Table 8 Solubility of Nitrofurantoin in various solvents

Sr. No.	Solvent	Solubility (%w/w)
1	Tween 20	13.42
2	PEG 400	10.62
3	Propylene glycol	8.74
4	Glycerin	4.75
5	Distilled water	0.0000041
6	Phosphate Buffer pH 6.8	0.0019

3.1.8. UV spectroscopy (determination of λmax)

The standard solution of Nitrofurantoin (10 µg/ml) shows maximum absorbance at 240nm wavelength in 0.1N HCl.

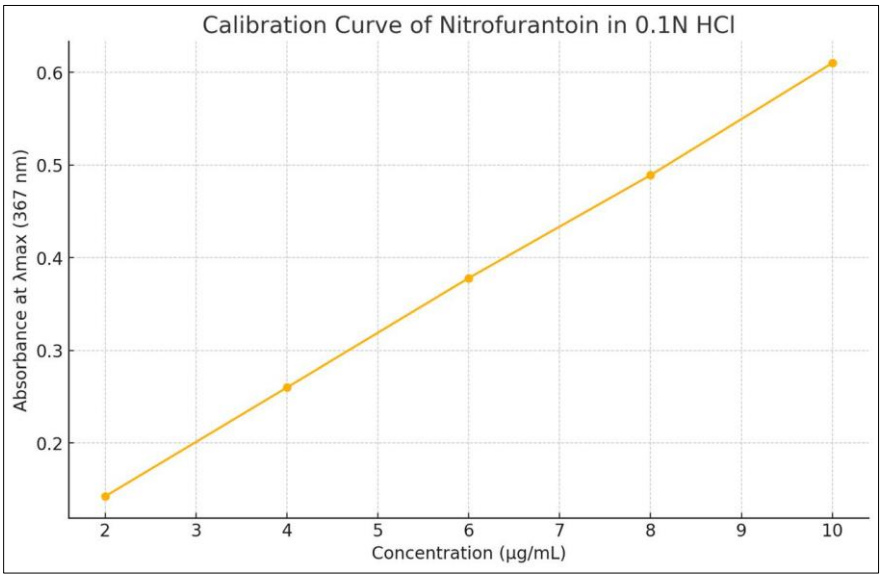

Figure 6 Calibration graph

Table 9 Absorption data of Nitrofurantoin in 0.1N HCl

Sr. No.	Concentration (µg/ml)	Absorbance
1	2	0.142
2	4	0.260
3	6	0.378
4	8	0.489
5	10	0.610

3.2. Pre-formulation studies of formulation

Formulae F1, F2, F3, F4, F5, F6, F7, F8 and F9 were proven to be acceptably flowing according to angle of repose, Carr's index and Hausner's ratio.

Table 10 Flowability parameters of nitrofurantoin liquisolid powder system

Formulation	Tap density	Bulk density	Angle of repose	Cars index	Hausner's ratio
F1	0.507± 0.011	0.424±0.013	27.92±1.26	16.38±2.41	1.20±0.02
F2	0.49±0.014	0.417±0.017	28.81±1.31	14.89±1.74	1.17±0.03
F3	0.513±0.010	0.445±0.012	29.90±0.95	13.25±1.23	1.15±0.02
F4	0.468±0.008	0.395±0.009	30.47±1.28	15.60±1.65	1.18±0.02
F5	0.481±0.006	0.419±0.008	30.05±1.10	12.91±0.98	1.15±0.01
F6	0.446±0.010	0.385±0.007	31.34±1.52	13.68±1.33	1.16±0.02
F7	0.527±0.013	0.439±0.012	32.71±1.68	16.71±1.79	1.20±0.03
F8	0.538±0.011	0.455±0.015	33.10±1.22	15.41±1.22	1.18±0.02
F9	0.511±0.009	0.421±0.011	26.88±1.06	17.61±1.28	1.21±0.01

3.3. Evaluation of liquisolid compacts

Table 11 Evaluation of liquisolid compacts

Formulation No.	Thickness (mm)	Diameter (mm)0	Hardness (kg/cm^2)	Weight Variation (g)
Control	5.5 ± 0.0	9.5 ± 0.0	5.92 ± 0.58	0.505 ± 0.0051
F1	5.5 ± 0.0	9.5 ± 0.0	5.10 ± 0.60	0.552 ± 0.0020
F2	5.5 ± 0.0	9.5 ± 0.0	4.90 ± 0.66	0.610 ± 0.0018
F3	5.5 ± 0.0	9.5 ± 0.0	5.12 ± 0.70	0.627 ± 0.0025
F4	5.5 ± 0.0	9.5 ± 0.0	4.75 ± 0.26	0.365 ± 0.0023
F5	5.5 ± 0.0	9.5 ± 0.0	5.02 ± 0.50	0.405 ± 0.0018
F6	5.5 ± 0.0	9.5 ± 0.0	4.62 ± 0.55	0.422 ± 0.0020
F7	5.5 ± 0.0	9.5 ± 0.0	4.95 ± 0.30	0.285 ± 0.0022
F8	5.5 ± 0.0	9.5 ± 0.0	4.98 ± 0.80	0.312 ± 0.0021
F9	5.5 ± 0.0	9.5 ± 0.0	5.08 ± 0.60	0.328 ± 0.0024

Table 12 Evaluation of liquisolid compacts

Formulation No.	Friability (%)	Disintegration Time (Sec)*	% Drug Content*	% Drug Release in 1 hr
Control	0.89	107.33 ± 1.38	101.22 ± 1.67	62.47
F1	0.30	55.80 ± 0.16	95.66 ±1.22	89.33607
F2	0.44	50.07 ± 1.35	97.34 ± 2.05	97.22951
F3	0.33	56.00 ± 0.07	95.24 ±2.8	91.84426
F4	0.24	58.00 ± 1.00	91.95± 1.98	80.04098
F5	0.48	62.33± 0.07	90.84± 1.67	73.18033

F6	0.54	58.00 ± 2.00	93.66 ± 2.41	82.15082
F7	0.55	55.77 ± 1.76	93.80 ± 1.93	87.66885
F8	0.50	51.43 ± 1.43	91.20 ± 1.54	77.13607
F9	0.53	55.67 ± 0.71	94.00 ± 2.25	84.26066

3.4. *In vitro* drug release

Table 13 *In vitro* drug release of all formulations

Time	F1	F2	F3	F4	F5	F6	F7	F8	F9	Control
0	0	0	0	0	0	0	0	0	0	0
5	25.35	31.6	14.64	18.24	13.53	12.57	13.26	10.2	12.9	10.1
10	37.02	40.8	25.53	28.83	19.8	19.89	21.66	14.13	19.11	14.5
15	43.2	51.53	37.65	41.13	25.56	32.16	27.51	20.43	21.66	18.97
20	56.13	60.13	47.73	46.53	32.04	42.51	37.83	25.14	27.57	22.5
25	62.49	69.33	57.21	52.56	42.48	56.01	46.89	35.43	39.33	30.01
30	69.25	78.69	64.35	58.53	51.69	61.53	57.6	44.91	49.14	39.48
45	82.26	88.86	78.01	64.83	61.8	70.83	63.05	55.5	58.47	49.01
60	92.67	97.5	88.53	76.15	73.51	79.92	70.8	71.21	68.1	62.47

3.5. Stability studies

Table 14 Stability studies of formulation (F2)

Evaluation parameter	Temperature(25±2ºC& 60±5%RH)	Temperature 40±2ºC & 75±5% RH		
	Before Stability Storage	After 10th Days	After 20th Days	After 30th Days
Hardness (Kg/cm^2)	4.83±0.11	4.83±0.11	8.82±0.09	4.82±0.12
Friability (%)	0.44±0.00	0.44±0.01	0.44±0.02	0.45±0.021
Weight Variation	598±0.01	598±0.01	598±0.01	598±0.01
Drug content (%)	97.34±2.05	97.34±2.02	96.62±0.06	96.75±0.12
Drug release (%)	97.22	97.12	97.02	96.89

4. Conclusion

The aim of the present study was to enhance the solubility and dissolution rate of Nitrofurantoin, a poorly water-soluble antibacterial agent, in the form of liquisolid compact tablets. Pre-formulation studies were conducted to confirm the identification and purity of the drug, and solubility studies concluded that Tween 20 increased the solubility of Nitrofurantoin vs. non -volatile solvents used in the study. By using Spirea's mathematical model, we developed several formulations by manipulating the drug concentration and ratio of carrier to coating materials to increase flowability and compressibility.

Of the formulations tested, F2 (10% drug in Tween 20, R = 20) was the most successful tablet with respect to hardness, immediate disintegration, uniformity of drug content, and dissolution. F2 yielded a total of 97.5% drug release over 60 minutes, which is a significant increase from the controlled amounts released. In summary, the enhanced dissolution

was mainly due to improved wetting, larger surface area, and molecular dispersion of the drug inside the formulation. Stability studies further indicated that the optimized formulation was stable -461- under accelerated conditions.

In conclusion, it has been shown that the liquisolid compact technique could be employed in a reliable and simple way for improving the dissolution and therefore potentially bioavailability of Nitrofurantoin. This study provides support for the use of liquisolid compact as a promising option for improving the effectiveness of poorly soluble oral drugs.

Compliance with ethical standards

Acknowledgments

We express our sincere gratitude to Dr. Datkhile S.V. for her invaluable guidance and support throughout this research. Her mentorship was instrumental in the successful completion of this study. We also extend our thanks to our institution for providing the necessary resources and facilities to conduct this research.

Disclosure of conflict of interest

The authors declare that they have no conflict of interest with the research work of any other authors cited in this manuscript,

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